IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Sean B. Carroll *et al.*
Serial No.: 10/662,918 Group No.: 1644
Filed: 09/15/03 Examiner: Kim, Yunsoo
Entitled: **Clostridial Toxin Disease Therapy**

APPEAL BRIEF
APPEAL NO.:

ATTENTION: Board of Patent Appeals and Interferences
Mail Stop - Appeals
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATE OF ELECTRONIC FILING

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being deposited with the U.S. Patent and Trademark Office, via EFS.

Dated: January 15, 2009

Traci E. Light

BPAI:

This Brief is in furtherance to the Notice of Appeal mailed by the Applicant on October 16, 2008 regarding the Advisory Action mailed July 17, 2008. A request for a one-month extension of time is submitted herewith.

This Brief is transmitted as a single copy as per the amended rules. [37 CFR § 41.37(a).]

This Brief contains these items under the following headings and in the order set forth below [37 CFR § 1.192(c)]

I. REAL PARTY IN INTEREST

The real party in interest is Ophidian Pharmaceuticals, Inc., 2800 South Fish Hatchery Road, Madison, WI 53711.

II. RELATED APPEALS AND INTERFERENCES

There are no related applications pending appeal.

III. STATUS OF CLAIMS

Claims 1, 3-13 and 15-21 are rejected and are currently appealed.

IV. STATUS OF AMENDMENTS

All amendments in the case have been entered.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The first independent claim (Claim 1) recites a method for administering an antibody reactive with *Clostridium perfringens* (pg 6 ln 19), **comprising** providing a subject (pg 5 ln 27), and an orally administrable solution (pg 5 ln 26-27) comprising avian antibody reactive with *Clostridium perfringens*, and orally administering said solution to said subject (pg 5 ln 28). Dependent Claim 3 recites that said solution is in the form of a nutritional formula (pg 6, ln 22). Dependent Claim 4 recites that said nutritional formula comprises infant formula (pg 6, ln 22). Dependent Claim 5, recited that said subject is an animal (pg 5 ln 22). Dependent Claim 6 recites that said administering is prophylactic (pg 5 ln 30). Dependent Claim 7 recites that said administering is therapeutic (pg 5 ln 26).

The second independent claim (Claim 8) recites a method for administering an antibody reactive with *Clostridium perfringens* (pg 6 ln 19), **consisting essentially of** providing a subject (pg 5 ln 27), and an orally administrable solution (pg 5 ln 26-27) comprising avian antibody reactive with *Clostridium perfringens*, and orally administering said solution to said subject (pg 5 ln 28). Dependent Claim 9 recites wherein said solution is in the form of a nutritional formula (pg 6 ln 22). Dependent Claim 10 recites wherein said nutritional formula comprises infant formula (pg 6 ln 22).

Dependent Claim 11 recites wherein said subject is an animal (pg 5 ln 22). Dependent Claim 12 recites wherein said administering is prophylactic (pg 5 ln 30). Dependent Claim 13 recites wherein said administering is therapeutic (pg 5 ln 26).

The third independent claim (Claim 15) recites a method for administering an antibody reactive with *Clostridium perfringens* (pg 6 ln 19), **consisting** of providing a subject (pg 5 ln 27), and an orally administrable solution (pg 5 ln 26-27) comprising avian egg antibody (pg 9 ln 8) reactive with *Clostridium perfringens*, and orally administering said solution to said subject (pg 5 ln 28). Dependent Claim 16 recites wherein said solution is in the form of a nutritional formula (pg 6 ln 22). Dependent Claim 17 recites wherein said nutritional formula comprises infant formula (pg 6 ln 22). Dependent Claim 18 recites wherein said subject is an animal (pg 5 ln 22). Dependent Claim 19 recites wherein said administering is prophylactic (pg 5 ln 30). Dependent Claim 20 recites wherein said administering is therapeutic (pg 5 ln 26). Dependent Claim 21 recites wherein said subject has not been treated to induce tolerance.

VI. GROUNDS OF REJECTION TO BE REVIEWED UPON APPEAL

A. Whether the Examiner has considered all of the claims and their limitations.

B. Whether the Examiner Relies On A Misunderstanding Of the Case Law.

C. Whether Claims 1 and 3-13 are properly rejected under 35 USC § 103(a) as allegedly being unpatentable over U.S. Pat. No. 4,748,018, in view of Uemura *et al.*, as evidenced by Merck Manual of Diagnosis and Therapy (17^{th} ed., 1999, p. 1176-1185).

D. Whether Claims 1, 5-8, 11-13,15 and 18-20 are properly rejected under 35 USC § 103(a) as allegedly being unpatentable over U.S. Pat. No. 4,689,299, in view of U.S. Pat. No. 4,550,019.

E. Whether Claims 3, 4, 9, 10, 16 and 17 are properly rejected under 35 USC § 103(a) as allegedly being unpatentable over U.S. Pat. No. 4,689,299, U.S. Pat. No. 4,550,019, and further in view of U.S. Pat. No. 4,748,018.

F. Whether the Examiner has properly considered the rebuttal evidence.

VII. ARGUMENT

A. The Examiner Has Failed To Consider All Of The Claims And All Of Their Limitations.

The Examiner's most recent rejection (mailed July 17, 2008) simply restates the (faulty) arguments used in the prior rejections. This may be seen by, for example, the failure of the Final Rejection of 07/17/2008 to even mention Claim 21 – which was included as a New Claim in the Applicants' response dated 4/11/2008. While the Summary page lists Claim 21 as a rejected claim, there is no basis offered in the body of the Final Office Action for the rejection, i.e. Claim 21 is not even listed among the claims that are allegedly obvious.

It would appear that the Examiner has simply cut and pasted prior arguments. The Examiner argues that "the claimed invention is not limited to the method for administering an antibody to the population without developing the tolerance." (See the Final Office Action, p.3). And yet, Claim 21 specifies that "said subject has not been treated to induce tolerance."

Moreover, Applicants submit that Claim 8 (which specifies "consisting essentially of") would exclude other steps, such as the step of inducing tolerance. The Examiner simply decides to treat "consisting essentially of" as equivalent to "comprising." (See Final Office Action, p.3). This is improper. In the present case novel characteristics are clear (oral antibody therapy for *C. perfringens*). Moreover, the Second Declaration of Dr. Stafford (at paragraph 5) makes a showing that the introduction of additional steps (weeks and months of inducing tolerance) would materially and negatively impact the claimed invention set forth in Claim 8.

B. The Examiner Misunderstands The Case Law

The extent to which the Applicants feel that prosecution of the present application has reached an impasse may be demonstrated by the Examiner's mere "cut and paste" approach to addressing the arguments offered by the Applicants in the previous response. The Applicants cannot agree that a verbatim recitation of arguments from one rejection (i.e. the Non-Final Rejection mailed 01/11/2008) in a subsequent rejection (i.e. the Final

Rejection mailed 07/17/2008) represents a good-faith attempt by the Examiner to evaluate this application on its merits.

In regard to the alleged obviousness of Claims 1 and 3-13, the following passage represents the only new piece of "analysis" provided by the Examiner in the Final Rejection mailed 07/17/2008:

> "It is reminded that the obviousness rejection is based on a combination of references and one cannot show unobviousness by attacking references individually."[1]

The Examiner cites to nothing in support of this statement. Applicants believe that the Examiner is taking the statement from MPEP 2145, part IV:

> One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

If so, the Examiner has made a mistake. The Examiner fails to realize that *In re Keller* was decided upon an affidavit that discussed only one of three cited references. Similarly, *In re Merck & Co.* supports a finding by the Federal Circuit that the presentation of a non-obviousness argument to only one cited reference (out a total of nine) is insufficient to overcome an obviousness rejection.

Thus, one may (of course) individually attack references in a combination – but each reference must be attacked, not just one among many. Stated another way, only where the applicants fail to address the remaining references in the combination is the Examiner's argument on point. Such is not the case here. Applicants attacked each reference in the combination:

> "The Examiner is reminded that the '018 Patent does not mention *C. perfringens*. The Uemura reference and the Merck reference do not teach oral therapy for *C. perfringens*. Applicants argued that there is nothing in the Uemura reference or Merck reference that would cause one skilled in the art to resort to the IMPRACTICAL teachings of the '018 Patent."

[1] Final Office Action, page 3, lines 11-13.

(See Applicants' response to the January 11, 2008 Office Action, p.7). Clearly, Applicants have not simply attacked one reference to the exclusion of the others in the combination. As such, the *In re Keller* and *In re Merck* cases do not apply. Therefore, the Examiner's reliance on this case law is misplaced.

C. Claims 1 And 3-13 Are NOT Properly Rejected Under 35 USC § 103(a) As Allegedly Being Unpatentable Over U.S. Pat. No. 4,748,018, In View Of Uemura *et al.*, As Evidenced by Merck Manual Of Diagnosis And Therapy (17th ed., 1999, p. 1176-1185).

1. Applicants' Central Argument Remains Unaddressed

Claims 1, 8 and 15 all require oral administration of avian antibodies. In the response mailed 10/26/2007 (at the bottom of page 6), Applicants challenged the Examiner's combination of the '018 Patent with the Uemura and Merck references by pointing out that common sense would dictate antibiotic treatment – not oral antibodies:

> "Thus, one skilled in the art would ask: do I want to use antibiotics or do I want to resort to this time-consuming method of the '018 Patent? Common sense dictates that antibiotics are the easier route than what is offered by the '018 Patent and thus the practical route for food poisoning. There is no rational underpinning to support the Examiner's combination or conclusion that an antibody based approach for *C. perfringens* is obviousness. One skilled in the art would simply view the '018 Patent approach to be not practical. (See Second Declaration of Dr. Stafford, paragraph 5)."

Thus, Applicants central argument (supported by the declaration) was that while antibiotics might be obvious, the particular references cited certainly did not make oral antibody therapy for *C. perfringens* obvious. The Examiner was reminded that the '018 Patent does not mention *C. perfringens*. The Uemura reference and the Merck reference do not teach oral therapy for *C. perfringens*. Applicants argued that there is nothing in the Uemura reference or Merck reference that would cause one skilled in the art to resort to the IMPRACTICAL teachings of the '018 Patent.

The only possibly responsive statement by the Examiner was the statement that in the Merck reference "antitoxin is used (p.1178, of record, in particular)." (which the

Examiner repeats in the Final Office Action, page 3). But, as argued in the last response, this completely misses the point! Dr. Stafford's Declaration specifically noted that the antitoxin treatment for tetanus discussed in the Merck document was NOT oral. (See the Second Declaration, paragraph 6). Turning to page 1178 (cited "in particular" by the Examiner), one finds antitoxin discussed in the context of tetanus only in the context of parenteral therapy (e.g. IM injections) – just as Dr. Stafford pointed out!

Applicants previously stressed (also on page 6 of the response) that the Merck reference provides a DIFFERENT solution for *C. perfringens*:

> "The Examiner is not free to ignore the fact that the Merck Manual suggests a different solution for *C. perfringens*, namely antibiotics."

The Examiner was reminded that he/she cannot rely on material that is OUT OF CONTEXT and ignore material that is IN CONTEXT. The antitoxin therapy of tetanus discussed in the Merck reference, since it is for a different organism and is NOT oral, is OUT OF CONTEXT. The treatment for *C. perfringens* – which is IN CONTEXT – is antibiotics. The Examiner cannot pick and choose bits of unrelated material, to the exclusion of the relevant teachings in the Merck reference:

> "It is impermissible, within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art."

In re Wesslau, 353 F.2d 238, 241, 147 USPQ 391, 393 (CCPA 1965) [Cited in *In re Hedges*, 228 USPQ 685, 687 (Fed. Cir. 1986)].

Thus, the central argument, that nothing in the Merck reference would cause someone skilled in the art to do anything except treat *C. perfringens* with antibiotic, has been side-stepped and remains unaddressed by the Examiner. This is fatal to the Examiner's obviousness rejection based on these references. There is nothing in the record that serves as a legitimate BASIS for combining the references. This is a critical pre-requisite; absent a basis for making the combination, the obviousness rejection cannot stand. *See In re Rouffet*, 149 F.3d 1350, 1359, 47 USPQ2d 1453, 1459 (Fed. Cir. 1998)

("the Board must identify specifically . . . the reasons one of ordinary skill in the art would have been motivated to select the references and combine them").

2. The '018 Patent Teaches Away

The 018 Patent does not teach anything about *C. perfringens*. Moreover, the 018 Patent requires that the mammal being tolerant to the antibody by virtue of having a history of consumption of antibody. This makes the teachings of the '018 Patent impractical (see Declaration of Dr. Stafford, paragraph 4) and undermines any notion that such teachings can be readily combined with anything else.

Indeed, the 018 teaches that the use of heterologous antibodies cannot otherwise be done safely:

> The failure of the immune system of an animal to respond to foreign protein is a condition known as immunological tolerance. Moreover, it is well known to those skilled in the art of immunology that mammals of a given species lack tolerance to antibodies from various animal species, including other mammalian species. *It is therefore apparent that heterologous antibodies obtained from alien species cannot be safely used to treat mammals*

(see the 018 Patent, DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS, first paragraph). This is an explicit statement in the cited art that indicates there is NO chance of success without tolerance. This teaches away from the presently claimed invention.

3. Uemura et al. Provides No Teachings Regarding Therapy

The Uemura et al. publication does not deal with therapy. As noted by Dr. Stafford, the paper provides no direct connection between serum antibody and exposure, and offers no insight or suggestion on the existence, role in disease resistance, or medicament value of luminal toxin antibodies (or any antibodies for that matter) in *C. prefringens* disease. (Declaration, paragraph 5). Accordingly, there is no basis for combining the references or asserting "it would be obvious."

D. Claims 1, 5-8, 11-13,15 And 18-20 Are NOT Properly Rejected Under 35 USC § 103(a) As Allegedly Being Unpatentable Over U.S. Pat. No. 4,689,299, In View Of U.S. Pat. No. 4,550,019.

1. The '299 Patent Teaches Away

The '299 patent focuses on the then emerging use of monoclonal antibodies as replacements for polyclonal antibodies (notably for therapy of acute bacterial toxicity such as tetanus and diphtheria). Numerous statements made by the '299 inventors emphasize the inadequacy of polyclonal antibodies. Thus, rather than supporting the Examiner's argument, it undermines it. The '299 patent repeatedly teaches away from the use of polyclonal antibodies.

> [Column 2; lines 43-46] Monoclonal antibodies are replacing conventional antisera in diagnostic laboratories and are providing new insights in medicine
>
> [Column 3; lines 9-18] Thus, the resulting antiserum reflects the contribution of **multiple antibody-secreting clones that contribute both desired and undesired antibodies**. [emphasis added] These undesirable antibodies must then be absorbed from the antiserum to prevent interference with its intended use. Conventional antisera is difficult to reproduce because individual animals respond unpredictably with varying proportions of antibody of different activity and specificity; therefore, supplies are often limited.
>
> [Column 3; line24-28] Hybridoma antibody technology . . . has the distinct **advantage** of allowing the use of complex unpurified antigens [emphasis added]
>
> [Column 9; lines 41-46, discussing the use of polyclonal antisera for tetanus treatment] A major **disadvantage** of equine anti-toxin antibodies is that their use can result in serum sickness . . . [emphasis added] For this reason, horse antisera are no longer prevalently in use . . . [Column 9; lines 53-63, here the inventors go on to suggest that human antisera would be a better alternative to heterologous antisera, but there remain problems with polyclonal therapy] While the risk of serum sickness is reduced by using human polyclonal antibodies, there are other inherent problems, in addition to expense, associated with their use. . . lot-to-lot variation . . . transferring contaminants and disease-causing agents . . . the need to immunize humans.
>
> [Column 11; lines 23-29, the inventors describe the methods and drawbacks of polyclonal treatment in diphtheria] Allergic sensitivity to horse serum proteins must nevertheless be assessed prior to administration of the antitoxin. Obviously, this can delay treatment. Moreover, lack of immediate allergic reaction does not

> negate the possibility of long term adverse reaction, such as serum sickness. Use of horse antisera poses the same disadvantages discussed for tetanus antitoxin . . .
>
> [Column 12; lines 23-35, the inventors teach the problems associated with polyclonal antibody production] This [monoclonal antibody therapy] is a distinct **advantage** over the traditional technique of raising antibodies in immunized humans and animals where the resulting sera contain **multiple antibodies of different specificities that vary in both type and titer with each animal** and, in individual animals, with each immunization. [emphasis added] Furthermore, animal sera require extensive purification to remove contaminants that can cause serum shock upon administration to humans; such procedures can add to the cost of traditional polyclonal antibodies. Even when human antisera are used, there may still be the problem of serum contaminants or inadequate supply.

The Examiner previously asserted that the disclosure in Columns 11 and 12 of the '299 Patent make obvious the instant invention. Quite the contrary, as shown above the '299 inventors make it quite clear that polyclonal antibody strategies should be avoided for their stated reasons. In the Final Office Action, the argument by the Examiner appears to have been dropped.

The Examiner also previously cited Table 1 of the '299 patent as anticipating our polyclonal antibodies. Applicants previously argued that this is incorrect and misleading. The paragraph referencing Table 1 discusses the applications were human monoclonal antibodies could be employed ([Column 11; lines 62-66] The invention encompasses the extension of the human-rodent hybridoma technique to the production of human monoclonal antibodies against other microbial [sic] toxins including, but not limited to, the exotoxins listed in Table 1 . . .). Once again, in the Final Office Action, this argument by the Examiner appears to have been dropped.

By pointing to the advantages of monoclonal antibodies over polyclonal antibodies, the '299 Patent teaches away from the polyclonal avian antibodies presently claimed:

> "A reference may be said to teach away when a person of ordinary skill, upon [examining] (sic) the reference, . . . would be led in a direction divergent from the path that was taken by the applicant."

Para-Ordnance Manufacturing v. SGS Importers International, 37 USPQ2d 1237,1241 (Fed. Cir. 1995) (quoting *In re Gurley*, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994)).

Clearly, one skilled in the art, upon reading the MANY statements in the '299 Patent (quoted above) about the advantages of monoclonal antibody technology and disadvantages of polyclonal antibodies, would be led in a direction AWAY from polyclonal antibodies. To underscore the nature of the antibodies claimed, Claim 15 has been amended to specify that the avian antibodies are "egg" antibodies, which are by nature polyclonal. Support for "egg" antibodies is found in numerous places in the specification, including but not limited to, page 9, lines 6-19.

Given the MANY statements (quoted above) in the '299 Patent against non-monoclonal approaches, this reference clearly CANNOT be combined with non-monoclonal art, which is what the Examiner has done. Such references are completely incompatible. Moreover, such statements (including but not limited to statements about "undesired antibody") indicate a belief that there is a poor likelihood of success.

For the first time, the Examiner attempts to argue against Applicants' teaching away argument by citing to passages in the '019 Patent (See Final Office Action, p.4). The Examiner argues that teachings in the '019 Patent indicate avian antibodies have advantages over other polyclonal antibodies, such as horse. Applicants submit that this argument is not relevant to what the '299 Patent teaches. In short, the Examiner cannot change what the '299 Patent teaches regarding monoclonal antibodies by citing language from another patent, such as the '019 Patent. Thus, the Examiner has not changed the fact that the '299 Patent teaches away.

2. The '019 Patent Does Not Teach Oral Administration

The Examiner attempts to combine the '299 Patent (which as noted above, teaches away from polyclonal antibodies) with the '019 Patent (which teaches the use of avian polyclonal antibodies). Because the '299 Patent teaches away, there is no basis for the combination.

Moreover, the '019 does not teach oral administration. Rather, it appears injections are contemplated:

> "When the immune system of an animal is challenged with an immunogen (e.g. by injection) to produce antibodies against an antigen having antigenic determinants corresponding to the immunogenic determinants of the immunogen,

> that is known as active immunisation; whilst the administration to an animal, e.g. by injection of antibodies extraneously produced, e.g. in a different animal in order to produce resistance against antigens for which the antibodies are specific, is known as passive immunisation."

(See '019 Patent, Description of the Invention, paragraph 5).

> "The resulting IgY antibodies after having been recovered from the egg yolk are converted into an injectable form and are then injected into the mammal in an immunising dosage. The concept of passively immunising mammals including humans with fowl egg IgY is considered novel per se."

(See '019 Patent, 12 paragraphs before the Description of the Preferred Embodiments). Thus, there is no teaching in the '019 Patent which supports the combination.

E. Claims 3, 4, 9, 10, 16 And 17 Are NOT Properly Rejected Under 35 USC § 103(a) As Allegedly Being Unpatentable Over U.S. Pat. No. 4,689,299, U.S. Pat. No. 4,550,019, And Further In View Of U.S. Pat. No. 4,748,018.

The Applicants have shown above that Claim 1, 8 and 15 are not obvious in view of the cited references. It is well settled patent law, that nonobviousness of an independent claim is imputed into any and all subsequent dependent claims:

> [D]ependent claims are nonobvious if the independent claims from which they depend are nonobvious.

In re Fritch, 972 F.2d 1260, 1266 (Fed. Cir. 1992). As such, the Examiner is respectfully requested to withdraw the pending rejection.

F. The Examiner Continually Fails To Consider ALL Of The Evidence

In a prior response mailed 10/26/2007 (see page 8), the Applicants noted the materials from the Arizona Department of Health (which was made of record in an Office Action dated 01/25/07) concerning *C. perfringens*. Applicants argued that the complete lack of oral therapy in the document is evidence of non-obviousness. The Examiner has continually failed to even acknowledge this evidence and argument. This is improper. The Examiner must address each and every piece of rebuttal evidence. Indeed, the

analysis must start over, as stated in *In re Rinehart*, 531 F.2d 1048, 1052, 189 USPQ 143, 147 (CCPA 1976), "[w]hen . . . evidence is submitted in rebuttal, the decision-maker must start over . . . An earlier decision should not, as it was here, be considered as set in concrete." See also *In re Piasecki*, 745 F.2d 1468, 1472, 223 USPQ 785, 788 (Fed. Cir. 1984) ("the examiner must consider all of the evidence anew."). Looking at the Final Office Action, this evidence is again not discussed. This is improper.

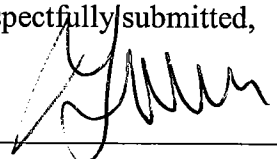
Conclusion

The Appellants submit that the Examiner has not made a *prima facie* case of obviousness for any of the claims discussed above. In fact, because the Examiner appears to have 1) ignored claims, 2) ignored claim language, 3) misconstrued the case law, and 4) repeatedly failed to address all the evidence, the Appellants believe that the Examiner has acted in an arbitrary and capricious manner. The Board is reminded that PTO decisions are reviewed using the standard set forth in the Administrative Procedure Act, 5 U.S.C. § 706. *Dickinson v. Zurko*, 527 U.S. 150, 154 (1999). Under that statute, actions are set aside that are arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law. Moreover, factual findings are set aside that are unsupported by substantial evidence. *In re McDaniel*, 293 F.3d 1379, 1382 (Fed. Cir. 2002).

Appellants submit that, with due consideration to all these factors discussed above, the patentability of Claims 1, 3-13 and 15-21 is evident.

For these reasons, the Applicants now appeal because it appears the Examiner has taken an arbitrary and intransigent position. It is submitted that the Examiner's rejections of Claims 1, 3-13 and 15-21 were erroneous, and reversal of these rejections is respectfully requested.

Respectfully submitted,



Dated: January 15, 2009

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VIII. CLAIMS APPENDIX

1. A method for administering an antibody reactive with *Clostridium perfringens*, comprising:
    a) providing:
        i) a subject; and
        ii) an orally administrable solution comprising avian antibody reactive with *Clostridium perfringens*; and
    b) orally administering said solution to said subject.

2. (Canceled).

3. The method of Claim 1, wherein said solution is in the form of a nutritional formula.

4. The method of Claim 3, wherein said nutritional formula comprises infant formula.

5. The method of Claim 1, wherein said subject is an animal.

6. The method of Claim 1, wherein said administering is prophylactic.

7. The method of Claim 1, wherein said administering is therapeutic.

8. A method for administering an antibody reactive with *Clostridium perfringens*, consisting essentially of the steps:
    a) providing:
        i) a subject; and
        ii) an orally administrable solution comprising avian antibody reactive with *Clostridium perfringens*; and
    b) orally administering said solution to said subject.

9. The method of Claim 8, wherein said solution is in the form of a nutritional formula.

10. The method of Claim 9, wherein said nutritional formula comprises infant formula.

11. The method of Claim 8, wherein said subject is an animal.

12. The method of Claim 8, wherein said administering is prophylactic.

13. The method of Claim 8, wherein said administering is therapeutic.

14. (Canceled)

15. A method for administering an antibody reactive with *Clostridium perfringens*, consisting of:
    a) providing:

i) a subject; and
ii) an orally administrable solution comprising avian egg antibody reactive with *Clostridium perfringens*; and

b) orally administering said solution to said subject.

16. The method of Claim 15, wherein said solution is in the form of a nutritional formula.

17. The method of Claim 16, wherein said nutritional formula comprises infant formula.

18. The method of Claim 15, wherein said subject is an animal.

19. The method of Claim 15, wherein said administering is prophylactic.

20. The method of Claim 15, wherein said administering is therapeutic.

21. The method of Claim 8, wherein said subject has not been treated to induce tolerance.

IX. EVIDENCE APPPENDIX

Attachment 1:

First Declaration Of Dr. Douglas C. Stafford

Attachment 2:

Second Declaration Of Dr. Douglas C. Stafford

PATENT
Attorney Docket No. **OPHD-08258**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	SEAN B. CARROLL, Ph.D. *et al.*		
Serial No.:	10/662,918	Group No.:	1644
Filed:	09/15/03	Examiner:	Kim, Y.
Entitled:	**CLOSTRIDIAL TOXIN DISEASE THERAPY**		

DECLARATION OF DR. DOUGLAS C. STAFFORD UNDER 37 C.F.R. § 1.132

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8(a)(1)(i)(A)

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being deposited with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, PO Box 1450, Alexandria, VA 22313-1450.

Date: May 24, 2007 By: Traci E. Light
TRACI E. LIGHT

Sir:

I, Douglas C. Stafford, under penalty of perjury, state that:

1. I was President and Chief Executive Officer of Ophidian Pharmaceuticals, Inc. at 5445 East Cheryl Parkway, Madison, WI 53711 ("Ophidian"). Ophidian was the original owner of the above-identified patent application.

2. I had supervisory responsibility for certain experimentation performed at Ophidian which has relevance to the subject matter in the above-referenced patent application. I have a Ph.D. degree in Immunology and was involved in the design and interpretation of studies described below.

3. During the 1990s, I supervised experiments where antibodies to Clostridium toxins were tested for the ability to protect against infection, i.e. these antibodies were administered prophylactically. Such an experiment can be found in an issued patent, U.S. Patent No. 5,762,934, a patent that shares some of the same lineage as the present case (both cases stem in part from U.S. Patent Application Ser. No. 07/985,321, filed Dec. 4, 1992). Example 9 (which is entitled In Vivo Protection Of Golden Syrian Hamsters From *C. difficile* Disease By Avian Antitoxins Against *C. difficile* Toxins A And B) shows that antibodies to a Clostridial toxin can be readily used prophylactically where (as with *C. perfringens*) the toxins are not automatically lethal. The basic experimental design was as follows:

> On day 1, each animal was orally administered 1.0 ml of one of the three antitoxin preparations (prepared in section (a) above) at the following timepoints: 0 hrs., 4 hrs., and 8 hrs. On day 2, the day 1 treatment was repeated. On day 3, at the 0 hr. timepoint, each animal was again administered antitoxin, as described above. At 1 hr., each animal was orally administered 3.0 mg of clindamycin-HCl (Sigma) in 1 ml of water. This treatment predisposed the animals to infection with *C. difficile.*

The results are described as follows:

> Treatment of hamsters with orally-administered toxin A and toxin B antitoxin (group CTAB) successfully protected 7 out of 7 (100%) of the animals from *C. difficile* disease. Treatment of hamsters with orally-administered toxin A antitoxin (group CTA) protected 5 out of 7 (71%) of these animals from *C. difficile* disease. Treatment using pre-immune IgY was not protective against *C. difficile* disease, as only 1 out of 7 (14%) of these animals survived.

Thus, Example 9 provides clear evidence that such an prophylactic approach works and, indeed, works well.

4. I have read U.S. Patent No. 4,748,018 cited by the Examiner. The 018 Patent teaches a method of passively immunizing a mammal against a condition caused by an antigen. However the invention requires the step of administering to the mammal immunizing amounts of an antibody obtained from a domesticated fowl which has been immunized against the antigen; the mammal being tolerant to the antibody by virtue of having a history of consumption of

antibody containing material derived from the egg of a fowl (emphasis added). If one followed the teaching of 018 there could be no medicament for human use since developing oral tolerance in humans is not commonly practiced, effective, or practical.

5. The Uemura, et al., paper cited merely provides extant knowledge that *Clostridium perfringens* responsible for food poisoning produce entertoxin. The paper further describes experiments to quantify the amount of SERUM antibody to type A toxin found in NORMAL persons. The paper offered no insight or suggestion on the existence, role in disease resistance, or medicament value of luminal toxin antibodies (or any antibodies for that matter) in *C. prefringens* disease. The authors could not even draw a clear line from antibody titers to the natural history of toxin mediated disease, specifically its possible role in disease prophylaxis. In fact the authors further confuse the issues by stating: [i]t is not possible at the present time to explain the high prevalence of enterotoxin antibody in human sera nor is the reason for the observed national difference known. Antibody production might be induced during acute *C. perfringens* food poisoning but could possibly also be due to prolonged absorption of enterotoxin in symptomless carriers who harbor high numbers of *C. perfringens* type A (page 471). According, the authors do not provide any information relevant to administration of an oral medicament.

Dated: MAY 22, 2007

By: _____
Douglas C. Stafford, Ph.D.

X. RELATED PROCEEDINGS APPENDIX

(No attachments are required for this Brief)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	SEAN B. CARROLL, Ph.D. *et al.*		
Serial No.:	10/662,918	Group No.:	1644
Filed:	09/15/03	Examiner:	Kim, Y.
Entitled:	**CLOSTRIDIAL TOXIN DISEASE THERAPY**		

SECOND DECLARATION OF DR. DOUGLAS C. STAFFORD UNDER 37 C.F.R. § 1.132

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8(a)(1)(i)(A)

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being deposited with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, PO Box 1450, Alexandria, VA 22313-1450.

Date: Oct 26, 2007 By: Traci E. Light

Sir:

I, Douglas C. Stafford, under penalty of perjury, state that:

1. I was President and Chief Executive Officer of Ophidian Pharmaceuticals, Inc. at 5445 East Cheryl Parkway, Madison, WI 53711 ("Ophidian"). Ophidian was the original owner of the above-identified patent application.

2. I had supervisory responsibility for certain experimentation performed at Ophidian which has relevance to the subject matter in the above-referenced patent application. I have a Ph.D. degree in Immunology and was involved in the design and interpretation of studies described below. I previously supplied a 132 Declaration in this matter.

3. As noted in my prior Declaration, I have read U.S. Patent No. 4,748,018 cited by the Examiner. The '018 Patent teaches a method of passively immunizing a mammal against a condition caused by an antigen. The '018 Patent further teaches that inducing tolerance to such antibodies would enable passive immunization. The '018 patent states, "[t]his tolerance occurs in mammalian individuals who have been previously fed a material containing antibodies from the heterologous fowl species" (emphasis added). Accordingly, the examiner's statement that "the '018 patent teaches the tolerance is developed by the subsequent administration of antibody (col. 4, lines 42-45)" (emphasis added) is in an incorrect reading of the '018 patent.

4. It should be understood in the '018 patent that induction of tolerance is an active, deliberate process that requires administration "over time." The '018 inventors state, "the immune system tolerance, which is a necessary condition for heterologous antibody administration, does not occur naturally, and must be built up in a mammal subject **over time** by the feeding of material containing fowl antibodies." (emphasis added). Such time involves weeks to months. Indeed, the immunology literature is filled with such examples of deliberate induction of tolerance in animals (10-15 day tolerance regime in rats; Journal of Immunology, 1993, 151:5751) and humans (19 day tolerance regime in humans; Journal of Immunology, 1994, 152:4663). The '018 patent itself recites in its Example 2 that tolerance is induced in recipient rabbits by feeding antibody for "30 consecutive days prior to injecting [antibody]." They further go on to say, "[f]or older animals and humans, the minimum time to acquire tolerance can be up to several months." Such evidence makes it clear that tolerance will not be induced in merely a matter of hours. Thus, the multiple administrations in Example 6 to which the Examiner refers ("The mice received . . . treatments . . . 1 hour before and ½ hour, 4 hours, and 8 hours after botulinal toxin administration") will not induce tolerance. Clearly, there is no support for the Examiner's statement that the present invention "implicitly requires developing tolerance as well." Tolerance could not have been relevant given the rapid time course of the animal experiments.

5. Clearly, the teaching of the '018 patent is completely counter to the strategy used in the instant invention. Practice of the therapeutic regimen of the instant invention does not require the

prior, deliberate administration of heterologous antibodies and the induction of tolerance. Quite the contrary, the requirement for induction of tolerance (which might be expected to take several weeks to months) would be a rather impractical prerequisite for an acute treatment for microbial toxicity.

6. The Merck manual cited by the examiner does not describe an antitoxin for toxic shock. Furthermore, the Merck manual only describes the use of clostridial antitoxins to botulinum and tetanus toxins and both of these are parenteral therapies (requiring intramuscular, intracutaneous, or intravenous administration). The treatments described for *C. perfringens* infections include only chemical antibiotics such as penicillin G or tetracycline (in contrast to antibodies of the instant invention). Thus, this reference does not point to a passive, oral antibody therapy for *C. perfringens*.

7. The Uemura, et al., paper cited merely provides extant knowledge that *Clostridium perfringens* responsible for food poisoning produce entertoxin. Uemura does not teach toxic shock produced by clostridial species is treatable by antitoxin therapy. This simply cannot be found in the paper. Thus, this reference also does not point to a passive, oral antibody therapy for *C. perfringens*.

Dated: Oct 23, 2007

By: _____
Douglas C. Stafford, Ph.D.

X. RELATED PROCEEDINGS APPENDIX

(No attachments are required for this Brief)